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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,604	07/28/2003	Gregg A. Hastings	PF185D1C2	4279

22195 7590 08/22/2006

HUMAN GENOME SCIENCES INC.
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EXAMINER	
SAOUD, CHRISTINE J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,604	HASTINGS ET AL.	
	Examiner	Art Unit	
	Christine J. Saoud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-29 and 32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-29, 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Seq. alignment 2 pgs.

DETAILED ACTION

Applicant's response of 15 June 2006 has been received and entered. Claims 1-20 and 30-31 have been canceled. Claims 21-29 and 32-36 are currently pending and under examination in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 15 June 2006 have been fully considered but are not persuasive.

Claim Rejections - 35 USC § 101 and 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21-29 and 32-36 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial credible asserted utility or a well established utility for the reasons of record in the previous Office action. The claimed invention is drawn to a protein with no apparent or disclosed specific and substantial credible utility.

Applicant argues at page 6 of the response that the specification asserts a specific biological role for the claimed polypeptides based on amino acid sequence homology to SCGF polypeptides. SCGF polypeptides are a family of growth regulators

comprising *cef*10/*cyr* 61, connective tissue growth factor and *nov*. Applicant argues that "SCGF polypeptides would be useful for 'wound healing and associated therapies concerned with re-growth of tissue ... for tissue remodeling such as restenosis ... and may also be employed to stimulate angiogenesis'." Applicant concludes that the specification asserts a specific biological role for SCGF polypeptides and "correlates this activity to specific deficiencies and/or conditions".

Applicant's arguments have been fully considered, but are not found persuasive. The specification teaches that the claimed proteins share 27% "homology" to members of the CCN family with the highest % similarity over a 29 amino acid stretch at 62% (see page 4, paragraph [0024]). When looking at % identity, the closest match to the CCN family is 8.6% amino acid sequence identity to *cef*10 (see attached sequence alignment). One of ordinary skill in the art would not accept 8.6% amino acid sequence identity as predictive of biological activity for a novel protein.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18: 34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, page 36). Similarly, Bork (2000, Genome Research 10: 398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially page 399). Such concerns are also echoed by

Doerks et al. (1998, Trends in Genetics 14: 248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15: 1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15: 132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12: 425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247: 1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (page 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of activity based on approximately 9% amino acid sequence identity to a member of a protein family.

Applicant argues at page 7 of the response that "the issue is whether an asserted utility is more likely than not true to one of ordinary skill in the art; a *reasonable correlation* between the disclosed biological activity and the asserted utility is sufficient." Applicant's argument has been fully considered, but is not persuasive. Applicant is correct in stating the issue, but the instant specification does not disclose a biological activity for the claimed invention. Instead, the instant specification asserts a biological activity for the claimed polypeptide based on approximately 9% amino acid sequence identity to a protein of the CCN family. Therefore, the issue is whether one of ordinary skill in the art would find it more likely than not that the claimed polypeptide would have a similar biological activity to the CCN family based on 9% amino acid sequence identity. Based on the teachings listed above, the answer is that one of ordinary skill in the art would not find it more likely than not that the claimed polypeptide has any particular biological activity because the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and 9% sequence identity would not be found persuasive to conclude anything regarding membership into a protein family or biological activity, absent evidence to the contrary. Contrary to Applicant's assertions, the fact pattern is directly analogous to that of *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility.

Applicant asserts at page 7 of the response that "the encoded polypeptides of the instant invention are members of the CCN growth factor family", however, the evidence presented in the instant specification fails to support this conclusion. At the time the instant invention was filed, this may have been the protein family with the closest amino acid sequence similarity, but this alone does not provide basis for assignment to the CCN protein family. As stated above, one of ordinary skill in the art would more likely than not doubt this assignment based on the extremely low degree of amino acid sequence identity (approximately 9%). Furthermore, post-filing art has found that the protein of the instant invention is an inhibitor of BMP molecules and is expressed in developing teeth and other ectodermal appendages such as hair as well as in renal collecting ducts. The post-filing art of Laurikkala et al. (Develop. Biol. 264: 91-105, 2003) suggests that ectodin (term coined in the art for the claimed protein) is an important regulator of the morphogenesis of ectodermal organs (see page 103, column 1, paragraph 2). The post-filing art fails to confirm any of the asserted utilities of the instant specification and the asserted utilities are not specific and substantial for the reasons of record, therefore, the rejection is being maintained. Since the instant specification does not disclose a credible "real world" use for the claimed invention, it is incomplete and, therefore, does not meet the requirements of 35 U.S.C. §101 as being useful.

Claims 21-29 and 32-36 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial credible asserted utility or a well established utility for the reasons set forth

above and in the previous Office action, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on Monday-Friday, 6AM-2PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud

Seq. alignment - attachment 2 pages

CEF/10

```
RESULT 5
A41428
CEF-10 protein precursor - chicken
C;Species: Gallus gallus (chicken)
C;Date: 03-Apr-1992 #sequence_revision 03-Apr-1992 #text_change 31-Dec-2004
C;Accession: A41428
R;Simmons, D.L.; Levy, D.B.; Yannoni, Y.; Erikson, R.L.
Proc. Natl. Acad. Sci. U.S.A. 86, 1178-1182, 1989
A;Title: Identification of a phorbol ester-repressible v-src-inducible gene.
A;Reference number: A41428; MUID:89145206; PMID:2537491
A;Accession: A41428
A;Status: preliminary
A;Molecule type: mRNA
A;Residues: 1-375
A;Cross-references: UNIPROT:P19336; UNIPARC:UPI0000127478; GB:J04496; NID:g211435; PID
C;Superfamily: IGFBP-related protein, CNN type

  Query Match             8.6%;  Score 95.5;  DB 2;  Length 375;
  Best Local Similarity   26.6%;  Pred. No. 0.42;
  Matches   34;  Conservative   22;  Mismatches   57;  Indels   15;  Gaps    7;

Qy         63 TGLD-RNTRVQVGCRELRSTKYISDGQC--TSISPLKELVCAGECL-----PLPVLPNWI 114
              ||:  | |     |: :: |:      |   | : ||:     :|       | ||   :
Db        240 TGISTRVTNDNPDCKLIKETRICEVRPCGQPSYASLKK---GKKCTKTKKSPSPVRFTYA 296

Qy        115 GGGYGTKYWSR--RSSQEWRCVN-DKTRTQRIQLQCQDGSTRTYKITVVTACKCKRYTRQ 171
              |     ||  :   |  : ||    :||| :|: :| || | |  : :: :|:|  |
Db        297 GCSSVKKYRPKYCGSCVDGRCCTPQQTRTVKIRFRCDDGETFTKSVMMIQSCRC-NYNCP 355

Qy        172 HNESSHNF 179
              |   :: |
Db        356 HANEAYPF 363
```

CYR61

```
RESULT 6
A35669
gene CYR61 protein precursor - mouse
C;Species: Mus musculus (house mouse)
C;Date: 28-Sep-1990 #sequence_revision 18-Nov-1992 #text_change 31-Dec-2004
C;Accession: A35669; I48319; S16446
R;O'Brien, T.P.; Yang, G.P.; Sanders, L.; Lau, L.F.
Mol. Cell. Biol. 10, 3569-3577, 1990
A;Title: Expression of cyr61, a growth factor-inducible immediate-early gene.
A;Reference number: A35669; MUID:90287146; PMID:2355916
A;Accession: A35669
A;Status: preliminary
A;Molecule type: mRNA
A;Residues: 1-379
A;Cross-references: UNIPROT:P18406; UNIPARC:UPI0000022DFF; GB:M32490; NID:g192909; PID
A;Note: the authors translated the codon GAT for residue 337 as Gln
R;Latinkic, B.V.; O'Brien, T.P.; Lau, L.F.
Nucleic Acids Res. 19, 3261-3267, 1991
A;Title: Promoter function and structure of the growth factor-inducible immediate earl
A;Reference number: I48319; MUID:91288203; PMID:2062642
A;Accession: I48319
A;Status: translated from GB/EMBL/DDBJ
A;Molecule type: DNA
A;Residues: 1-379
A;Cross-references: UNIPARC:UPI0000022DFF; EMBL:X56790; NID:g50632; PIDN:CAA40109.1; P
A;Note: the authors did not translate the codon for residue 108
```

```
A;Note: the authors translated the codon GAT for residue 337 as Gln
C;Genetics:
A;Gene: CYR61
A;Introns: 21/3; 93/1; 208/1; 279/3
C;Superfamily: IGFBP-related protein, CNN type
F;99-166/Domain: von Willebrand factor type C repeat homology

  Query Match             8.5%;  Score 95;  DB 2;  Length 379;
  Best Local Similarity   23.9%;  Pred. No. 0.47;
  Matches   37;  Conservative   26;  Mismatches   76;  Indels   16;  Gaps    6;

Qy          41 PAHPSSNSTLNQARNGGRHFSNTGLDRNTRV---QVGCRELRSTKYISDGQCTS--ISPL 95
               | |      : |  :  :   : |   :|||      || :: |:      |     | |
Db         219 PLHAHGQKCIVQTTSWSQCSKSCGTGISTRVTNDNPECRLVKETRICEVRPCGQPVYSSL 278

Qy          96 KELVCAGEC-----LPLPVLPNWIGGGYGTKYWSR--RSSQEWRCVND-KTRTQRIQLQC 147
               |:     :|       | ||   : |     ||  :   |  : ||    :||| ::: :|
Db         279 KK---GKKCSKTKKSPEPVRFTYAGCSSVKKYRPKYCGSCVDGRCCTPLQTRTVKMRFRC 335

Qy         148 QDGSTRTYKITVVTACKCKRYTRQHNESSHNFESM 182
               :||   :  : :: :|||       ||:|    |:
Db         336 EDGEMFSKNVMMIQSCKCNYNCPHPNEASFRLYSL 370
```